REMARKS

After the addition of claim 89, claims 38-43 and 89 are pending.

The amendment to claim 38 is merely editorial.

The insertion of "pattern" in and deletion of "the main" from claims 39-40 are editorial and would not narrow the scope of the amended claim recitations.

The replacement of "Furier" with "Fourier" and deletion of "the following" from claims 41-42 are editorial and would not narrow the scope of the amended claim recitations.

Descriptive support for the new claim 89 can be found in page 11, line 6, of the specification.

Claim Objections

Applicants respectfully traverse the objection of claims 39-43 as substantial duplicate of claim 38. The Office Action objects to claims 39-43 because the Office Action alleges, citing MPEP 706.03(k), that claims 39-43 cover the same thing as claim 38 despite a slight difference in wording. Applicants respectfully disagree.

Applicants note that applicants have the right to restate (i.e., by more than one claim) the invention in a reasonable number of ways. See MPEP 706.03(k). Claim 38 is drawn to BOS-Na Form II. Claim 39 is drawn to a crystalline sodium salt of benzisoxazole methane sulfonic acid characterized by four XRD peaks recited in the claim. Thus, for a crystalline sodium salt of benzisoxazole methane sulfonic acid to literally meet all the limitations of claim 39, the crystalline sodium salt of benzisoxazole methane sulfonic acid only requires to have an XRD pattern having the four peaks recited in claim 39. The literal scope of claim 39 is different than that of claim 38. Similarly, claims 40-43 differ in literal scope from claim 38. Applicants have the right to cover the invention in a reasonable number of ways by presenting claims having different number of limitations. Claims 39-43 are not substantial duplicate of claim 38. Withdrawal of the claim objections is requested.

Claim Rejections -- 35 U.S.C. 112, Second Paragraph

Applicants respectfully traverse the indefiniteness rejection of claims 38-43.

Claim 38 was rejected because claim 38 does not provide any powder X-ray diffraction data. Applicants are free to be their own lexicographer. MPEP 2173.05(a) III. Based on the disclosures in the specification, one skilled in the art would know the meaning of BOS-Na Form II recited in claim 38.

Claims 39 and 40 were rejected because they do not recite at least 10 XRD peaks. The position taken by the Office Action is based on a citation from a book by Brittain: "the USP general chapter on X-ray diffraction states that the identity is established if the scattering angles of the ten strongest reflections obtained for an **analyte** agree to within +/- 0.20 degrees with that of the **reference material**..." (emphasis added). Applicants note that the requirement of at least 10 strongest X-ray diffraction reflections is for identifying an

unknown in comparison with a known reference polymorphic material. Since the chemical nature of the "analyte" is not known before the identification procedure, Brittain puts forth a proposition that matching at least 10 strongest X-ray diffraction reflections within +/- 0.20 degrees is required for identifying the crystalline form of the unknown compound. However, claims 39 and 40 are not directed to any chemical compound. Instead, claims 39 and 40 are directed to a crystalline sodium salt of benzisoxazole methane sulfonic acid. Since the chemical compound involved is already known before the identification procedure, claims 39 and 40 should not be required to recite at least 10 XRD peaks. Coupled with the term "crystalline sodium salt of benzisoxazole methane sulfonic acid" in the preamble and the XRD peaks recited in claims 39 and 40, one skilled in the art would know the metes and bound of claims 39 and 40.

Claims 41-43 were rejected because these claims contain no X-ray diffraction data. Applicants respectfully traverse the rejection because a crystalline form can be identified with physical properties other than the X-ray diffraction data. According to J. Bernstein, IR spectroscopy has been one of the most widely used methods for investigating the propensity of materials to form polymorphs and Fourier transform IR spectroscopy is clearly the current method of choice (see J. Bernstein, *Polymorphism in Molecular Crystals*, pages 125-131, Clarendon Press, Oxford, 2002, attached; especially page 125, the second paragraph in Subsection 4.5 Infrared spectroscopy, the first two sentences). Claims 41 and 42 recite the FTIR peaks sufficient to characterize the crystalline sodium salt of benzisoxazole methane sulfonic acid covered by claims 41 and 42. Applicants submit that one skilled in the art would know the meaning of the claim recitations of claims 41 and 42 and would know the metes and bound of these claims.

Claim 43 depends on claim 38. As discussed above, claim 38 is definite. The meanings of the claim recitations in claim 43 would be clear to one skilled in the art.

Withdrawal of the indefiniteness rejections of claims 38-43 is requested.

Provisional Obviousness Type Double Patenting Rejections

I. Applicants respectfully traverse the provisional rejection of claims 38-43 on the ground of obviousness type double patenting over claims 2-4 and 10-12 of U.S. Application No. 10/288,135 (hereinafter the '135 application). Claims 2-4 and 10-12 of the '135 application are directed toward a crystalline sodium salt of benzisoxazole methane sulfonic acid characterized by at least the XRD peaks recited in claim 2 of the '135 application.

The Office Action takes a position that claims 2-4 and 10-12 of the '135 application anticipate the instant claim 38 because the term "Form II" recited in claim 38 fails to offer any demarcation of the crystalline sodium salt of benzisoxazole methane sulfonic acid Form II from the crystalline sodium salt of benzisoxazole methane sulfonic acid Form IV according to claims 2-4 and 10-12 of the '135 application. Applicants respectfully disagree because, in view of the disclosure of the XRD properties in the specification, "Form II" is sufficient to

demarcate the crystalline sodium salt of benzisoxazole methane sulfonic acid according to the instant claim 38 from the crystalline sodium salt of benzisoxazole methane sulfonic acid Form IV according to claims 2-4 and 10-12 of the '135 application. See MPEP 2173.05(a) III. With the XRD information concerning Form II disclosed in the specification, a person skilled in the art would readily recognize that some of the XRD peaks in the XRD pattern disclosed in the specification for Form II according to the instant claim 38 do not match, within 0.2 degrees two theta, the XRD peaks for Form IV recited in claims 2-4 and 10-12 of the '135 application. For instance, the peaks at 5.3 and 21.3 ± 0.2 degrees two theta are not found among the XRD peaks recited in claims 2-4 and 10-12 of the '135 application.. The existence of polymorphs, if any, of any compound is unpredictable. For instance, Guillory stated in Brittain, *Polymorphism in Pharmaceutical Solids*, 1999, Marcel Dekker, Inc., that at the moment it is not possible "to predict, with confidence, that a particular crystalline packing arrangement is the most stable that is likely to be found" and "the developmental scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found" (the second full paragraph, page 185, in a Chapter entitled *Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids*). If it is difficult to predict how many solid forms of a drug are likely to be found, it would even be more difficult to predict that a particular solid form is likely to be found. There would not be any suggestion in the prior art that the crystalline sodium salt of benzisoxazole methane sulfonic acid of claims 2-4 and 10-12 could be modified to form the crystalline sodium salt of benzisoxazole methane sulfonic acid Form II of the instant claim 38. Thus, applicants submit that claims 2-4 and 10-12 of the '135 application would not render obvious the instant claim 38.

The Office Action also takes a position that claims 2-4 and 10-12 of the '135 application render obvious the instant claims 39-43 because claims 2-4 and 10-12 differ from the instant claims 39-43 only in the physical property recited in the claims. The Office Action indicates that the instant claims 39-43 would have been obvious over claims 2-4 and 10-12 of the '135 application because claims 39-43 merely are directed to a crystalline sodium salt differing from the crystalline sodium salt of claims 2-4 and 10-12 merely by forms and physical properties innate to the form. The Office Action relies on the court decision in *In re Cofer*, 148 USPQ 268 (CCPA 1966), and a Board decision in *Ex parte Hartop*, 139 USPQ 525 (Bd. Pat. App. 1962) for its obviousness conclusion. However, applicants note that the court in *In re Cofer* already overruled the broad proposition put forth by the Board in *Ex parte Hartop* that "merely changing the form, purity or another characteristic of an old product, the utility remaining the same as that of the old product, does not render the claimed product patentable." The Office Action's obviousness conclusion is based on an incorrect interpretation of case law. Claims 2-4 and 10-12 of the '135 application are directed to a crystalline sodium salt of benzisoxazole methane sulfonic acid which differs from the crystalline sodium salt of benzisoxazole methane sulfonic acid according to the instant claims 39-43. For instance, the properties recited in claims 2-4 and 10-12 of the '135 application are different from the properties recited in the instant claims 39-

43. Coupled with the knowledge in the art, a person skilled in the art would not have any motivation, suggestion or guidance of modifying Form IV in claims 2-4 and 10-12 of the '135 application to arrive at the crystalline sodium salt of the instant claims 39-43.

Withdrawal of the obviousness double patenting rejection of claims 38-43 over claims 2-4 and 10-12 of the '135 application is requested.

II. Applicants respectfully traverse the provisional rejection of claims 38-43 as obviousness-type double patenting over claims 28-31 of copending U.S. Application No. 10/662966 (hereinafter the '966 application). Claims 28-31 of the '966 application are directed to a crystalline form of the sodium salt of benzisoxazole methane sulfonic acid. The Office Action asserts that claims 28-31 of the '966 application render obvious the instant claims 38-43 because the sodium salt of benzisoxazole methane sulfonic acid according to claims 28-31 and the crystalline sodium salt of benzisoxazole methane sulfonic acid according to the instant claims 38-43 are of the same pure substance differing only in arrangements and/or conformations of the molecule. The Office Action states that mere difference in physical property is well known conventional variation for the same pure substance and is thus prima facie obvious. Applicants respectfully disagree. It is known that different crystalline forms of the same substance can have different physical properties. But the fact that the physical properties may differ between the crystalline forms of a compound does not necessarily make it easier to predict the number of crystalline forms that the compound may exist in or to predict whether a certain crystalline form of the compound would exist. The differences in the physical properties are insufficient to support an obviousness conclusion.

The Office Action also relies on the court decision in *In re Cofer* and the Board decision in *Ex parte Hartop* to support its obviousness type double patenting rejection. However, as discussed above, *Ex parte Hartop* was overruled by *In re Cofer*, which invalidates the broad proposition of the unpatentability of changed forms of an old product.

Withdrawal of the provisional obviousness-type double patenting over claims 28-31 of the '966 application is requested.

Claim Rejections -- 35 U.S.C. 102

I. Applicants respectfully traverse the anticipatory rejections, under 35 U.S.C. 102(b), of claim 38 over US 4,172,896 (hereinafter the '896 patent) or FR 2,428,033, which is the French equivalence of the '896 patent according to Derwent. Both the '896 patent and FR 2,428,033 disclose the preparation of crude crystalline sodium salt of benzisoxazole methane sulfonic acid by a process comprising heating, with stirring, 3-bromomethyl-1,2-benzisoxazole in methanol with sodium sulfite in water, followed by concentration under reduced pressure and recrystallization from methanol, wherein the crystalline residue was washed with diethyl ether to give the crude crystalline sodium salt of benzisoxazole methane sulfonic acid (see Example 1 in the '896 patent and FR 2,428,033). The Office Action takes a position that claim 38 was anticipated by the crude crystalline sodium salt of benzisoxazole

methane sulfonic acid prepared in Examples 1 of the '896 patent and FR 2,428,033 because the term "BOS-Na Form II" recited in claim 38 fails to demarcate the claimed product from the crude crystalline sodium salt of benzisoxazole methane sulfonic acid prepared in the '896 patent and FR 2,428,033 (since they share the same compound name, sodium salt of benzisoxazole methane sulfonic acid). However, the Patent Office has neglected the fact that claim 38 is directed to the "crystalline sodium salt of benzisoxazole methane sulfonic acid (BOS-Na) Form II" having the characteristics and properties disclosed in the instant specification for BOS-Na Form II. There is no evidence that the crude crystalline salt of benzisoxazole methane sulfonic acid prepared in the '896 patent and FR 2,428,035 had the same characteristics and properties as BOS-Na Form II. Applicants also note that the crude crystalline salt of benzisoxazole methane sulfonic acid in the '896 patent and FR 2,428,035 was not prepared with a process involving the reaction of an anhydride and sulfuric acid to form acyl sulfate in the presence of ethyl acetate, followed by reacting the acyl sulfate with 1,2-benzisoxazole-3-acetic acid, and then raising the pH with NaOH to precipitate BOS-Na Form II as disclosed in page 10, lines 1-6, of the instant specification. Applicants submit that there is no evidence that the crude crystalline sodium salt of benzisoxazole methane sulfonic acid prepared in the '896 patent and FR 2,428,035 was BOS-Na Form II.

II. Applicants also respectfully traverse the anticipatory rejection, under 35 U.S.C. 102(e), of claim 38 over US 6,677,458 (hereinafter the '458 patent). The '458 patent discloses a process of preparing the sodium salt of benzisoxazole methane sulfonic acid comprising the steps of: 1) sulfonating 1,2-benzisoxazole-3-acetic acid using chlorosulfonic acid and dioxane in methylene chloride and then adding sodium hydroxide; and 2) isolating the sodium salt of benzisoxazole methane sulfonic acid from an aqueous solvent, preferably, by salting out with sodium chloride and cooling or by evaporation (column 4, lines 36-49). The process disclosed in the '458 patent differs from the process of preparing BOS-Na Form II disclosed in page 10, lines 1-6, of the instant specification in that the sulfonation of the 1,2-benzisoxazole-3-acetic acid involves the chlorosulfonic acid/dioxane complex, not the acyl sulfate formed in situ from the reaction of an anhydride and sulfuric acid in the presence of ethyl acetate. There is no evidence that the sodium salt of benzisoxazole methane sulfonic acid prepared by the process of the '458 patent is the crystalline sodium salt of benzisoxazole methane sulfonic acid (BOS-Na) Form II recited in claim 38. Withdrawal of the anticipatory rejection is requested.

Claim Rejections -- 35 U.S.C. 103

Applicants respectfully traverse the obviousness rejection of claims 39-43 over one of three cited primary references (US 4,172,896, FR 2,428,033 or US 6,617,458) and a secondary reference (Brittain, *Polymorphism in Pharmaceutical Solids*, 1999, Marcel Dekker, Inc.).

The '896 patent, FR 2,428,033 or the '458 patent differs from claims 39-43 at least in not disclosing a crystalline sodium salt of benzisoxazole methane sulfonic acid having the characteristics and properties recited in claims 39-43.

The Office Action takes a position that claims 39-43 were obvious over the '896 patent, FR 2,428,033 or the '458 patent and Brittain because of the following reasons.

(1) Brittain discloses in pages 1-2 that many pharmaceutical solids exhibit polymorphism, wherein polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations.

(2) The crystalline sodium salt of benzisoxazole methane sulfonic acid according to claims 39-43 merely differ from the known crystalline sodium salt of benzisoxazole methane sulfonic acid of the '896 patent, FR 2,428,033 or the '458 patent by forms and that the physical properties are innate to the forms. The Office Action asserts that there is nothing unobvious about the innate nature of a drug in exhibiting polymorphism because many solids exhibit polymorphism. The Office Action also asserts that, citing pages 178, 179 and 219 of Brittain, it is recognized in the art that the innately existed different polymorphs will display different physical properties such as XRD pattern, and just because it is different does not merit the new polymorph patentability.

(3) Brittain, in pages 1-2, as one having ordinary skill in the art, stated "that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable."

(4) According to *In re Cofer* and *Ex parte Hartop*, a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable.

(5) "Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain, p. 1-2), i.e. prima facie obvious."

Applicants respectfully disagree with the reasoning of the Office Action in support of its obviousness rejections. Just because many solid pharmaceuticals are known to exhibit polymorphism does not necessarily mean that the crystalline sodium salt of benzisoxazole methane sulfonic acid would exhibit polymorphism. Applicants submit that it is legally erroneously for the Office Action to assert that there is nothing unobvious about the innate nature of a drug in exhibiting polymorphism because many solids exhibit polymorphism. As discussed above, the existence of polymorphs, if any, of any compound is unpredictable. According to a chapter authored by Guillory in Brittain's textbook, *Polymorphism in Pharmaceutical Solids*, it is not possible "to predict, with confidence, that a particular crystalline packing arrangement is the most stable that is likely to be found" and "the developmental scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found" (the second full paragraph, page 185, in a Chapter entitled *Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids*). If it is difficult to predict how many solid forms of a drug are likely to be found, it would even be more difficult

to predict that a particular solid form is likely to be found. Given the art recognized unpredictability of polymorphism, applicants contend that claims 39-43 would not have been obvious over the '896 patent, FR 2,428,033 or the '458 patent and Brittain.

From the disclosures in the '896 patent, FR 2,428,033 or the '458 patent and Brittain, one of ordinary skill in the art would not reasonably predict that the crystalline sodium salt of benzisoxazole methane sulfonic acid exhibits polymorphism and would not reasonably predict that the crystalline sodium salt of benzisoxazole methane sulfonic acid according to claims 39-43 exists. In addition, the prior art cited by the Examiner does not teach or render obvious a process for preparing the crystalline sodium salt of benzisoxazole methane sulfonic acid according to claims 39-43. For instance, there was no suggestion in the cited prior art that the process to make the crystalline sodium salt of benzisoxazole methane sulfonic acid of the '896 patent, FR 2,428,033 or the '458 patent could be modified to make the crystalline sodium salt of benzisoxazole methane sulfonic acid according to claims 39-43. Thus, claims 39-43 would not have been obvious over the '896 patent, FR 2,428,033 or the '458 patent and Brittain.

The Office Action's reliance on the assertions in pages 178, 179 and 219 of Brittain that just because a new polymorph is different in terms of physical properties does not merit the new polymorph patentability is misplaced. This is because patentability is a legal determination to be ultimately made by a judge, and Brittain being may be a person of ordinary skill in the art was not qualified in determining whether a new polymorph is patentable or not. By the same token, the Office Action was wrong in relying on the assertion in pages 1-2 of Brittain, who may be a person having ordinary skill in the art, "that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable."

The Office Action's reliance on *In re Cofer* and *Ex parte Hartop* is also erroneous. As discussed above, *In re Cofer* already overruled the broad proposition put forth in *Ex parte Hartop* that changed forms of an old product are unpatentable. Examiner Anderson's attention is directed to the attached decision of the Board in *Ex parte Gala*, 2002 WL 851814 (Bd. Pat. App. & Interf.), which objected to the examiner's reliance on *Ex parte Hartop* and reversed the obviousness rejection of a claim directed to a polymorph of a known compound characterized by three powder XRD peaks over the prior art disclosing a different polymorph of the same compound without any XRD data disclosed because the prior art does not suggest the claimed polymorph and does not disclose or render obvious a method for making the claimed polymorph. Applicants also would like to direct Examiner Anderson's attention to the attached decision of the Board in *Ex parte Polniaszek*, 2003 WL 22282265 (Bd. Pat. App. & Interf.), which concerns a U.S. patent application examined by Examiner Anderson. In *Ex parte Polniaszek*, 2003 WL 22282265 (Bd. Pat. App. & Interf.), the Board reversed an obviousness rejection, over the prior art disclosing the amorphous form of a compound, of a claim directed to a polymorph of the same known compound reciting the melting point, because the Examiner had not established that the prior art even recognized that the known

compound exists in different polymorphic forms, that the prior art teaches this specific polymorph as claimed, or that there is a known or obvious way to manufacture the specific polymorphic form claimed. The Board emphasized in *Ex parte Polniaszek* that, according to *In re Cofer* and *In re Ochiai*, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995), reliance on *per se* rules of obviousness is legally incorrect and must be stopped. The reasoning used by Examiner Anderson in the instant application that new polymorphs of an old compound are *prima facie* obvious just because the new polymorphs are merely different forms of the old compound and that the new polymorphs "must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hygroscopicity[], recovery or prevention of precipitation etc." (see page 13, of the Office Action) is akin to a *per se* rule of *prima facie* obviousness. Reliance on such *per se* rule of *prima facie* obviousness must be stopped according to the Board in *Ex parte Polniaszek*.

Conclusion

In the event that there remains only minor issues that can be dealt with via a telephone interview, the Examiner is urged to call the undersign to discuss that to expedite the prosecution.

If the filing of this paper is deemed not time, applicants petition for an appropriate extension of time under 37 CFR 1.136. The petition fee under 37 CFR 1.17 and any other fees that may be required in relation to this paper can be charged to Deposit Account No. 11-0600.

Respectfully submitted,

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Dated: June 28, 2006

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Attachments: Petition for Extension of Time;
J. Bernstein, *Polymorphism in Molecular Crystals*, pages 125-131, Clarendon Press, Oxford, 2002;
J.K. Guillory, *Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids*, in H.G. Brittain, *Polymorphism in Pharmaceutical Solids*, 1999, Marcel Dekker, Inc., pages 183-187;
Ex parte Gala, 2002 WL 851814 (Bd. Pat. App. & Interf.);
Ex parte Polniaszek, 2003 WL 22282265 (Bd. Pat. App. & Interf.)